·综 述·

钠 - 葡萄糖耦联转运体 2 抑制剂治疗糖尿病肾病研究进展

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摘要：钠 - 葡萄糖耦联转运体 2 抑制剂（sodium-glucose linked transporter-2 inhibitor，SGLT-2i）是一种目前临床常用的口服降糖药，通过抑制肾小管葡萄糖重吸收、增加尿糖排泄以降低血糖水平，同时增加尿钠排泄，发挥降压、减轻体质量等作用，可多途径治疗糖尿病肾病（diabetic nephropathy，DN）。现简要归纳 SGLT-2i 在 DN 发生发展中的作用、机制及疗效等，旨在为临床提供一定参考。

关键词：钠 - 葡萄糖耦联转运体 2 抑制剂；糖尿病肾病；作用机制
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Advances in the treatment of diabetic nephropathy with sodium-glucose linked transporter-2 inhibitor

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Abstract: Sodium-glucose linked transporter-2 inhibitor (SGLT-2i) is a commonly used oral hypoglycemic agent in clinical practice, which reduces blood glucose by inhibiting renal tubule glucose reabsorption and increasing urinary glucose excretion, while increasing urinary sodium excretion. It plays the role of reducing blood pressure and reducing body mass, and treats diabetic nephropathy (DN) in multiple ways. This article briefly summarized the role, mechanism and clinical efficacy of SGLT-2i in the occurrence and development of DN, aiming to provide some reference for clinical practice.

Key words: sodium-glucose linked transporter-2 inhibitor; diabetic nephropathy; action mechanism

糖尿病肾病（diabetic nephropathy，DN）是一种由糖尿病（diabetes mellitus，DM）引起的慢性肾脏病（chronic kidney disease，CKD），亦是 DM 患者发生心血管疾病（cardiovascular disease，CVD）和死亡的重要原因[1]。DN 临床特征为持续进展的蛋白尿和（或）肾小球滤过率（glomerular filtration rate，GFR）进行性下降。DN 发病机制复杂，目前认为与糖代谢紊乱、血流动力学异常、氧化应激、炎性反应、细胞因子参与及遗传等因素有关[2]。

DN 早期防治十分重要，目前的主要治疗策略包括生活方式干预（控制体质量、锻炼及戒烟等）和控制血糖、血压及胆固醇水平［包括肾素 - 血管紧张素 - 醛固酮系统（renin-angiotensin-aldosterone system，RAAS）抑制剂、钠 - 葡萄糖耦联转运体 2 抑制剂（sodium-glucose linked transporter-2 inhibitor，SGLT-2i）及他汀类药物等］，可帮助延缓疾病进展，提高生活质量[3]。其中，SGLT-2i 是一类新型口服

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降糖药，由于其优秀的降糖效果及心肾保护作用[4]，已成为 DN 一线治疗用药，近年来受到高度重视。

1 SGLT-2i 改善 DN 患者代谢指标

1.1 SGLT-2i 对血糖及胰岛功能的影响

降糖治疗可延缓 DN 病程进展。SGLT-2i 可通过阻断位于近曲小管的 SGLT-2，抑制葡萄糖重吸收，使肾小管最大葡萄糖转运速率降低[5]，进而降低肾糖阈，增加尿糖排泄，降低糖化血红蛋白水平[6]，改善胰岛 β 细胞功能，增加胰岛素敏感性[7]。又因 SGLT-2i 的降糖作用不依赖于胰岛素，故低血糖发生风险低[8—9]。对于 CKD 患者，由于其尿糖排出减少，SGLT-2i 的降糖效果并不明显[10]。

1.2 SGLT-2i 对体质量及脂肪代谢的影响

研究显示，使用 SGLT-2i 治疗 6 ～ 12 个月，DN 患者体质量平均减轻 2 ～ 4 kg[11]。低血糖及相对低胰岛素状态可刺激胰高糖素分泌，脂肪细胞氧化分解代偿性增加，生成更多酮体，β- 羟丁酸水平升高，热量缺口导致脂肪减少和体质量减轻[12—14]。而酮体氧化可改善心肌细胞供能模式及心肌效率，是 SGLT-2i 治疗心力衰竭（heart failure，HF）的重要机制[15]。动物试验显示，对 2 型 DM（type 2 diabetes mellitus，T2DM）模型大鼠使用 SGLT-2i，可增加其 β- 羟丁酸水平，在急性心肌梗死（acute myocardial infarction）状态下介导肾脏尼克酰胺腺嘌呤二核苷酸磷酸氧化酶蛋白表达，减少氧化应激，从而发挥肾脏保护作用[16]。

1.3 SGLT-2i 对血压及尿酸的影响

高血压（hypertension）是 CKD 的独立危险因素，降低血压可有效减缓疾病进展。SGLT-2i 可帮助尿钠排泄，降低患者血容量并长期维持于较低水平，进而减少循环容量[17]。SGLT-2i 可增加红细胞压积，改善血管压力，进而发挥降压作用[18]。多项研究显示，SGLT-2i 可降低收缩压、舒张压，进而减少 DN、脑血管疾病和 HF 患者的住院风险[19—21]。

在体质量指数较高和基线血压较高的 DN 患者中，SGLT-2i 治疗期间血压降幅较对照组更大[22]。研究显示，SGLT-2i 可抑制近曲小管对尿酸盐的吸收[23]。此外，恩格列净（empagliflozin）可改善 DM 患者动脉硬化，达格列净（dapagliflozin）可改善 T2DM 患者的内皮功能障碍，在一定程度上降低血压[24—25]。同时，SGLT-2i 与钙通道阻滞剂、β 受体阻滞剂有协同降压作用，但与噻嗪类利尿药无协同作用[26]。

2 SGLT-2i 对肾脏的直接影响

2.1 SGLT-2i 对管球反馈（tubuloglomerular feedback，TGF）的影响

肾脏高滤过状态是 DN 经典的病理生理改变，在 T1DM 患者中发生率为 10% ～ 67%，在 T2DM 患者中发生率为 6% ～ 73%[27]，可能与入球小动脉、出球小动脉张力改变密切相关，多种血管活性物质参与其中，导致促炎症细胞因子激活、蛋白尿及肾脏疾病。

在高血糖状态下，SGLT-2 活性增加，钠和葡萄糖重吸收增加，并减少对致密斑的钠输送，引起致密斑细胞释放的单磷酸腺苷减少，腺苷合成减少。腺苷可与腺苷 A1 受体结合，触发血管平滑肌细胞内钙离子水平升高，在近曲小管发挥收缩血管的作用，是 TGF 的主要介质[28—29]。TGF 减弱导致肾小球入球动脉舒张、肾脏高灌注和肾脏高滤过状态，SGLT-2i 可阻断这种过度重吸收，并恢复钠向致密斑和 TGF 递送，增加腺苷合成，从而收缩入球小动脉并减弱超滤[30]。多项研究显示，恩格列净能显著改善 T1DM 患者肾脏高灌注、高滤过状态[31—33]。另外，达格列净可帮助 T2DM 患者舒张出球小动脉，改善肾脏高滤过[34]。

2.2 SGLT-2i 对 RAAS 的影响

在高血糖状态下，肾素在血浆和细胞局部过表达，导致血管紧张素（angiotensin，Ang）Ⅱ生成增加[35]，促使肾小球出球小动脉收缩并出现肾小球内高压，Ang Ⅱ可促进活性氧（reactive oxygen species，ROS）过量产生，而 ROS 可诱导线粒体功能障碍[36]，并刺激醛固酮释放，进一步激活氧化应激、促炎症和促纤维化通路。Ang 转换酶抑制剂和 Ang 受体阻

滞剂类药物可通过扩张出球小动脉，进而减少肾小球超负荷，然而由于肾素代偿性升高亦会扩张入球小动脉，使肾小球仍处于超滤状态，无法恢复 TGF，故 RAAS 阻断不能完全阻止 DN 发生、发展 [37]。

SGLT-2i 可帮助恢复 TGF，抑制 RAAS 激活和醛固酮释放，减轻肾脏氧化应激、炎症和纤维化。在 DN 患者使用 SGLT-2i 治疗早期，由于一过性血容量减少，可导致 RAAS 代偿性激活，肾素和醛固酮水平升高，平均在治疗 6 个月后上述指标恢复至基线水平 [38]，但 SGLT-2i 并不会长期影响全身 RAAS 活性 [39]。一项针对 T2DM 合并 DN 大鼠的研究证实达格列净可降低尿 Ang Ⅱ和 Ang 原，抑制肾内 RAAS 活性 [40]。

2.3 SGLT-2i 对促红细胞生成素（erythropoietin，EPO）的影响

糖代谢紊乱会刺激肾小管上皮细胞过度吸收相关代谢应激产物，可能触发产生 EPO 的成纤维细胞转化为肌成纤维细胞，造成血清 EPO 水平降低，促进肾小球和内皮纤维化，导致肾功能损伤 [41]。SGLT-2i 可减少钠钾泵能量消耗，缓解近曲小管上皮细胞代谢应激，改善肾脏氧合，修复成纤维细胞，增强 EPO 释放，继而增强造血功能，升高红细胞压积，促进达到生酮状态，有利提供能量，改善线粒体功能 [42—44]。

研究显示，使用恩格列净治疗 1 个月后，观察组 EPO 水平显著升高，这与血细胞比容增加相关 [45]。达格列净亦被证明可增加 T2DM 患者 EPO 和红细胞压积，这种作用与抑制铁调素和调节铁调节相关蛋白有关 [46]。SGLT-2i 相关红细胞压积增加被认为是这类药物提供的心血管和肾脏保护作用的的重要中介效应 [47]。

2.4 SGLT-2i 对炎症及细胞因子的影响

高血糖刺激 ROS 过度释放，促进细胞氧化应激，导致晚期糖基化终末产物（advanced glycation end product，AGE）生成、多元醇旁路及己糖胺通路激活等，而 AGE 激活肾细胞中的核因子（nuclear factor，NF）-κB，参与表达 DN 进展的促炎和促纤维化基因和生长因子，高血糖亦会增加细胞外基质蛋白，促进肾小球硬化 [48]。SGLT-2i 对肾脏的保护作用也可归因于抗炎途径，减少局部 ROS 产生，并伴内皮功能的改善 [49]。相关生物标志物的变化反映氧化应激和晚期糖酵解终产物减少 [50—51]。

3 SGLT-2i 治疗肾病相关循证临床研究

目前，SGLT-2i 的心血管结局研究（cardiovascular outcome study，CVOT）结果均已公布，证实其对心血管重要获益，同时将肾脏事件作为次要结局研究，提示对肾脏的积极作用。

EMPA-REG OUTCOME 证实恩格列净使 DM 伴心血管高风险患者的 DN 发生率或恶化率降低 39%。恩格列净组 GFR 在停药后逆转，提示 GFR 与药物使肾脏血流动力学改变的相关性更大。VERTIS CV 对 T2DM 伴冠状动脉粥样硬化性心脏病（coronary atherosclerotic heart disease，CHD）患者展开研究，艾拓格列净（ertugliflozin）组与安慰剂组肾病结局无显著差异 [52]。调整肾脏复合终点后，艾拓格列净组较安慰剂组肾脏复合终点发生率低 [53]，且可有效延缓蛋白尿进展，持续减慢 GFR 下降幅度。CANVAS 和 CANVAS-R 对 T2DM 伴 CHD 患者或合并 2 种以上高危心血管风险的 T2DM 患者展开研究，结果显示，卡格列净组肾脏不良结局及蛋白尿进展风险降低。DECLARE-TIMI 58 纳入 T2DM 合并 CVD 或具有 CVD 风险的患者，结果显示，达格列净组肾脏事件发生率、GFR 持续降低、终末期肾病（end-stage renal disease，ESRD）发生率及死亡率明显低于安慰剂组 [54]。

以上 4 项 CVOT 试验研究人群略有差异，部分试验复合肾脏疾病结局相似，且 80% 的受试者在基线时已接受 DN 的标准治疗，可能会对肾脏事件产生不同程度影响 [55]。

CREDENCE 结果显示，T2DM 合并肾功能异常、蛋白尿肾功能不全高危患者使用卡格列净较安慰剂可降低 30% 主要终点风险，且 GFR 30 ～ 45 ml/（min·1.73m^2）的卡格列净组受试者肾脏和心血管不

良结局发生风险较低[56]。DAPA-CKD 的 CKD 受试者使用达格列净较安慰剂主要终点风险显著降低。EMPA-KIDNEY 的 CKD 4 期患者使用恩格列净较安慰剂能更有效降低肾脏病进展或心血管事件死亡的复合终点及全因住院率，且与是否合并 DM 或基础 GFR 水平无关。以上 3 项研究都因中期分析疗效显著提前终止，说明 SGLT-2i 对 DN 及非 DM 的 CKD 患者具有可观的肾脏保护作用。

4 结语

综上，SGLT-2i 在降糖同时，有显著的肾脏保护作用，可改善 DN 预后，国内外指南均推荐 SGLT-2i 作为 T2DM 合并 DN 一线用药。SGLT-2i 治疗 DN 机制复杂，潜在机制和通路相关研究仍需展开进一步研究，为扩大适应证提供依据，且可为临床提供更多 DN 个体化治疗方案给予参考。

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